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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/647,057	NAGARAJA ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *12-15,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/3/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response

1. Applicant's response to restriction requirement filed on 10/11/05 is acknowledged.

Election

2. Applicant's election of claims 1- 11 and 16-17 drawn to isolated nucleic acid sequence SEQ.ID.NO: 8 with traverse is acknowledged.

The traversal is on the ground(s)that searching of SEQ ID NO: 9- 14 does not present an undue burden on the Office because, SEQ ID NO: 8 contains each of SEQ ID NO: 9-14 as a sub-sequence thereof. As noted in the specification, each of SEQ ID NO: 9-14 are a fragment of or truncated version of SEQ ID NO: 8. Applicants state that MPEP 803.04 recites that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction.

This is not found persuasive because there is nothing on the record that these inventions are not patentably distinct. As to the question of burden of search is merely one indication of the burdensome nature of the search involved. While search is not unduly burden on the Examiner, each invention is examined based on its merits and enablement.

The examiner reviewed MPEP 803.04 and noted "absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141". It is noted that SEQ.ID.NO: 8 is a multigene operon containing 9726 bp while SEQ.ID.NO: 9-14 are overlapping regions of the full length gene. Each sequence is encoding a polypeptide having a specific function. Some polypeptides could be used for assays and some can be used for therapy and some can be used for detecting infection. In addition, it is known in the

immunology field that one could make single chain antibodies or "diabodies" having several specificities for a single polypeptide. Therefore, it is proper to restrict different regions of a full-length gene. Further, up to 10 sequences may be searched under certain circumstances as seen fit by the Director. However, this is not the normal practice.

Status of claims

3. Claims 1-17 are pending

Claims 1- 11 and 16-17 are elected. However, claim 17 is drawn to non-elected invention, SEQ.ID.NO: 9-14. Therefore, it is withdrawn from the elected invention. Hence claims 1-11 and 16 are under examination.

Claims 12-15 and 17-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on 10/11/05.

Priority

4. This application 10/647057 is a DIV of 09/841,786 04/24/2001 PAT 6,669,940 which is a CIP of 09/558,257 04/25/2000 ABN.

Information Disclosure Statement

5. Information Disclosure Statement filed on 9/03/03 is acknowledged and a signed copy is attached to this Office action.

Drawings

6. The drawings filed on 8/23/03 are accepted by the examiner.

Specification - Informalities

7. Applicant is advised to update the status of the priority documents whether pending, patented or abandoned.

Claim Rejections - 35 USC § 112 first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-11and 16 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the revised guidelines on written description available at www.uspto.gov (O.G. published January 30, 2001). This is a written description rejection.

Claims 1-10 are drawn to an isolated nucleotide sequence and an expression vector comprising /having a nucleotide sequence having at least about 50%, 60%, 75%, 87%, 95% sequence homology with a sequence that is a truncated form of SEQ ID NO. 8.

Claim 16 is drawn to an isolated nucleotide sequence which differs from that of a nucleotide sequence having at least about 50% sequence homology with a sequence that is a truncated form of SEQ ID NO. 8 due to a mutation event selected from the group consisting of point mutations, deletions, insertions and rearrangements.

Recitation of "a recombinantly derived nucleotide sequence or a nucleic acid sequence comprising a truncated form of SEQ ID No. 8 is interpreted as a nucleic acid sequence which comprises a part of SEQ.ID.NO: 8 + unlimited/unknown sequence.

Claims 1-11 and 16 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. This is a written description rejection.

Claims are drawn to an isolated polynucleic acid comprising a sequence having at least 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO: 8, an isolated polynucleic acid which differs from that of SEQ.ID.NO: 8 due to a mutation selected from the group consisting of point mutation, deletions, insertions and rearrangements and a recombinant nucleotide sequence that encodes a polypeptide comprising a truncated form of SEQ.ID.NO: 8.

The specification describes as part of the invention, isolation of *Fusobacterium necrophorum* leukotxin A25 gene, its nucleotide sequence is expressed in E.coli. The immunoreactive clones containing the leukotoxin open reading frame (designated lktA) are depicted in FIG. 1. Inverse PCR was used to extend the cloned region to allow completion of the sequence of the lktA open reading frame. The 11,130 bp sequence of F. necrophorum DNA contained one complete and two partial ORFs. The upstream (orfB) partial ORF comprises the first 1,018 bp. The lktA ORF initiates 16 bp downstream of the lktB ochre codon. The leukotoxin determinant is 9,726 bp (SEQ.ID.NO:8) and encodes the protein of 3,241 amino acids with an overall molecular weight of 335,956. The protein has substantial hydrophobic character (FIG. 5) and possesses 14 regions with sufficient hydrophobic character and is a secreted toxin in *F. necrophorum*. However, the specification fails to teach an isolated polynucleic acid or a recombinant polynucleic acid comprising a sequence having at least 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO: 8 and an isolated polynucleic acid which differs from that of SEQ.ID.NO: 8 due to a mutation selected from the group consisting of point mutation, deletions, insertions and rearrangements (examiner is considering these as variants and hereafter referring them as variants of SEQ.ID.NO:8) with a reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See

page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116). Therefore, an isolated polynucleic acid or a recombinant polynucleic acid comprising the nucleic acid sequence, SEQ.ID.NO: 8 meets the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below:

The specification fails to teach variants of SEQ.ID.NO: 8 and is noted that the claimed nucleic acid do not exist as an invention independent of their function (secreted leukotoxin). The actual relevant identifying characteristics of each claimed variants of SEQ.ID.NO: 8 can only be determined empirically by actually making every nucleic acid variant and testing each to determine whether such a variant having the leukotoxin properties of the full length protein encoded by SEQ.ID.NO: 8. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention and its function. This specification does not teach such, and the art is devoid of teaching variants of SEQ.ID.NO: 8. There is no written description support for variants of SEQ.ID.NO: 8 as claimed. In addition, an isolated nucleic acid comprising (open language) a sequence SEQ.ID.NO: 8 plus unlimited and unknown amino acids would result in an unknown nucleic acid without sufficient structure and completely lacking identifying characteristics such as function, i.e. having leukotoxin activity. The specification fails to disclose any deletion or change in nucleic acid sequence, SEQ.ID.NO: 8 to obtain said variants that could be used to correlate between toxin production and ability to induce abscesses in the presence or absence of antitoxin antibody. . The specification does not describe any use of said variants as claimed (comprising, open language) in identifying strains of *Fusobacterium that produce (i.e., secreted) leukotoxin* and do not meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d

1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, the specification fails to teach variants of SEQ.ID.NO: 8 and does not satisfy the written description guidelines because the claimed variants have not been disclosed in this application. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

10. Claims 1-11 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleic acid or a recombinant polynucleic acid comprising the nucleic acid sequence SEQ.ID.NO: 8 does not reasonably provide enablement for an isolated polynucleic acid or a recombinant polynucleic acid comprising a sequence having at least 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO: 8 and an isolated polynucleic acid which differs from that of SEQ.ID.NO: 8 due to a mutation selected from the group consisting of point mutation, deletions, insertions and rearrangements. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Scope of enablement requires that the specification teach those in the art how to make and use the invention commensurate with the scope of the claimed invention without undue experimentation and includes an analysis of: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

With regard to %identity, the specification is not enabled for polynucleic acid / recombinant polynucleic acid which have 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO: 8 and an isolated polynucleic acid which differs from that of SEQ.ID.NO: 8 due to a mutation selected from the group consisting of point mutation, deletions, insertions and rearrangements because it is unclear to one skilled in the art what sequences are embraced by the claim and what point mutation, deletions, insertions and rearrangements have been done to SEQ.ID.NO: 8. If it is unclear to one skilled in the art what sequences are embraced by a claim which is based on a specification to determine percent homology/identity/similarity and modifications which would give rise to variants of SEQ.ID.NO: 8, the specification is non-enabling, since one skilled in the art would not be able to make and use those sequences without undue experimentation.

Applicant has not set forth which nucleic acid (s) can be deleted or inserted or substituted in the polynucleic acid SEQ.ID.NO: 8 to give rise to polynucleic acids which have an amino acid at least 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO 8. After these alterations or modifications whether the polynucleic acid variant can still retain the activity as presently claimed is not set forth clearly in the specification. The specification provides guidance and direction with regard to an isolated polynucleic acid/recombinant polynucleic acid comprising the nucleic acid sequence as set forth in the

SEQ.ID.NO: 8 (pages 9, 44-48), which is designated as BSBSE. However, the specification fails to teach variants of polynucleic acids /recombinant polynucleic acids which have 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO: 8.

It is well known that for proteins (encoded by nucleic acid), for example, even a single amino acid change can destroy the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Further, specification is silent on how to make these polynucleic acid/ recombinant polynucleic acid that have 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO 8. Applicant failed to give direction to what modifications have been done to SEQ.ID.NO: 8 to give rise to variants. What changes would have an adverse effect on the function of peptide encoded by variants is not predictable. It is known in the art that derivatives or variants, which are obtained by substitutions, deletions, or modifications, alter the function of the protein. The amino acid sequence of a protein encoded by nucleic acid determines its structural and functional properties, predictability of which changes can be tolerated and still retain activity (i.e., leukotoxin activity) requires a knowledge of and guidance with regard to which modifications are tolerated (i.e. expected intolerant to modification), and detailed knowledge of the ways in which the protein structure encoded by nucleic acid relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (Bowie et al. Science, Vol. 247: 1990; p. 1306; p. 1308) and is well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within

the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in protein and the result of such modifications is unpredictable based on the instant disclosure. The specification does not support the broad scope of the claims, which encompass variants of SEQ.ID.NO: 8. The specification provides essentially no guidance as to, which of the essentially infinite possible choices is likely to be successful.

With regard to function of a protein encoded by said polynucleic acid comprising a sequence homology with 50%, 60%, 75%, 87% and 95% with SEQ.ID.NO 8, Houghten et al. (Vaccines, 1986, Edited by Fred Brown: Cold Spring Harbor Laboratory) teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polynucleic acid will alter antigenic determinants and therefore affect antibody production (p. 21) as well as antibody binding. Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al. teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the variants that retain immunodominant regions and immunological activity if the regions have been altered.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed polynucleic acids in a manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions or partial sequence thereof that would encompass a biologically active variants as presently claimed. The scope of the claims must bear a reasonable correlation with the scope of

enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the nucleic acid sequence is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim Rejections - 35 USC 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-11 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Struck et al 1998 (U.S.Patent # 5,804,190).

Struck et al discloses recombinant DNA sequences coding for hemolysin toxin, recognized by anti-leukotoxin antibody in a western blot analysis (Claims, Column 8, lines 65-67). The disclosed polynucleic acid sequence read on the broadly claimed polynucleic acid comprising a sequence having at least 50%, 60%, 75%, 87% and 95% sequence homology with a sequence SEQ.ID.NO: 8, an isolated polynucleic acid which differs from that of SEQ.ID.NO: 8 due to a mutation selected from the group consisting of point mutation, deletions, insertions and rearrangements and a recombinant nucleotide sequence because any five nucleic acid of the disclosed sequence are 100% identical with the claimed a nucleic acid sequence (for example position 55-60 of the claimed SEQ.ID.NO:8 is identical with position 368-373 of figure 1A of Struck et al) Thus the prior art anticipated the claimed invention.

Remarks

13. No claims are allowed.

Conclusion

14. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.

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